EXECUTIVE SUMMARY

Background:

Numerous epidemiologic time series studies have shown generally consistent associations of outdoor particulate matter (PM) air pollution with cardiovascular hospital admissions and mortality. However, the pathophysiological mechanisms and causal pollutant components driving these associations are unclear. The present research is driven by the possibility that the time series associations may be due to airway deposition of airborne ultrafine particles and traffic-related pollutant components, followed by an increase in thrombogenic and inflammatory activity in the blood, and by adverse effects on cardiovascular function. This research relates to the Board's function in establishing air quality standards to protect human health. There have been no other studies to our knowledge conducted in California among vulnerable individuals on the acute cardiovascular health effects of exposures near subject residences to size-fractionated particles and to particle characteristics linked to general air pollutant sources and components.

Methods:

We conducted a comprehensive exposure assessment study and PM monitoring effort for a repeated measures panel study aimed at evaluating acute cardiovascular health effects of exposure to ultrafine PM. This project is to largely supplement the exposure assessment for an NIH, NIEHS funded study (grant no. ES-012243) entitled "Ultrafine Particulate Matter & Cardiorespiratory Health." Indoor and outdoor air pollution monitors were deployed under this CARB-AQMD funded exposure assessment effort to provide continuous air pollutant concentrations, as well as data on PM composition and redox activity. Modeling efforts specific to this proposal include PM source characterization, and additional repeated measures statistical analyses of the relationship between health outcomes and supplemental air pollutant measurements.

Under funding from NIH, we followed 64 nonsmoking elderly individuals with coronary artery disease (CAD) living in four retirement homes in the Los Angeles Air Basin of California (2 studied in Jul 2005 through Feb 2006, and 2 studied in Jul 2006 through Feb 2007). Each subject was to be followed for a total of 12 weeks in two 6-week seasonal periods (warm and cold). Each Friday, blood samples were obtained for biomarkers of inflammation including plasma interleukin-6 (IL-6), tumor necrosis factor-α and its receptor (sTNF-RII), and C-reactive protein (CRP). We also measured a biomarker of platelet activation, soluble platelet selectin (sP-selectin). Biomarkers of erythrocyte antioxidant activity included glutathione peroxidase-1 and superoxide dismutase (funded by funds to the Southern California EPA PM Center, Project 4). Over 10 days, we also monitored subjects' cardiovascular function with ambulatory electrocardiographs (ECG, to assess possible cardiac ischemic with ST segment depression) and ambulatory blood pressure monitors.

Supplemental air pollutant measurements funded under this contract included concurrent hourly indoor and outdoor concentrations of $PM_{2.5}$ mass and $PM_{2.5}$ elemental and organic carbon (EC-OC), and pollutant gases (NO_2, NO_x, and CO). At outdoor sites only, we measured hourly black carbon (BC) and ozone (O_3). Additional data from the NIH-funded study included hourly indoor and outdoor particle number (PN) concentrations (dominated by ultrafine PM), and size fractionated PM: quasi-ultrafine mode <0.25 μm ($PM_{0.25}$), accumulation mode 0.25-2.5 μm ($PM_{0.25\text{-}2.5}$), and coarse mode 2.5-10 μm ($PM_{2.5\text{-}10}$). Using this and other data, we also estimated primary and secondary organic carbon (OC_{pri}, SOC), and indoor EC, OC_{pri}, SOC, and PN of outdoor origin. We present results of the assessment of health impacts of the NIH-funded PM exposures here only to provide a more comprehensive picture of associations. Under this contract, we also conducted *in vitro* testing to assess redox activity in concentrated fine ($PM_{2.5}$) and ultrafine ($PM_{0.25}$) particle suspensions collected at indoor and outdoor sites with biosamplers constructed specifically for this task.

We analyzed the relationship of 10-day ambulatory cardiovascular outcomes and 12-weekly systemic (blood) biomarkers of inflammation and erythrocyte antioxidant activity to indoor and outdoor concentrations of EC, total OC (and OC_{pri}, SOC fractions), $PM_{2.5}$ mass, PN, and criteria pollutant gases, and to redox activity of PM using *in vitro* bioassay results. We analyzed data with mixed effects models adjusted for potential confounders.

Results:

Exposure assessment work provided a comprehensive view of indoor and outdoor exposure relations. We found that vehicular sources showed the highest contribution among the apportioned sources for both indoor and outdoor particles at all sites. The contribution of mobile sources to indoor levels was similar to their corresponding outdoor estimates, thus illustrating the significance of these sources on indoor PM concentrations.

The *in vitro* redox assay results revealed considerable differences between individual samples collected at any given site during a given weekly 2-day sample collection period. There were also differences between seasonal phases and community sites, but this was significant only for ultrafine PM, not fine PM. Differences between mean indoor and outdoor DTT and DHBA activity were found between seasons and sites. An analysis of the relation between DTT and DHBA activity and blood biomarkers was largely nonsignificant for $PM_{2.5}$ in year 1 subjects and $PM_{0.15}$ in year 2 subjects.

The analysis of biomarkers revealed that primary combustion markers (EC-BC, OC_{pri}, CO, NO_x-NO_2) were positively associated with inflammatory biomarkers and platelet activation and inversely associated with erythrocyte antioxidant enzymes (N=578). PN and $PM_{0.25}$ were more strongly associated with biomarkers than $PM_{0.25\text{-}2.5}$. Biomarker associations were stronger during cooler periods when only OC_{pri}, PN, and NOx were higher, suggesting that pollutant components and/or nanoparticles that increase during colder weather and air stagnation are important. We found weaker associations for sTNF-RII and CRP among subjects taking the anti-cholesterol drug, statin, which is known to reduce systemic inflammation and oxidative stress. We found weaker associations for sP-selectin among subjects taking the platelet aggregation inhibitor, clopidogrel. Associations were stronger for indoor exposures to EC and PN of outdoor origin than uncharacterized indoor exposures, suggesting that outdoor air pollution was important.

We found positive associations of hourly ambulatory systolic and diastolic blood pressure with exposure to outdoor home $PM_{2.5}$, BC, EC, OC, and to a lesser extent with exposure to outdoor CO and NO_x, but not PN. The strongest association was for OC, especially estimated fossil fuel combustion fraction (OC_{pri}). Associations were increasingly stronger from last 4-hr out to 9-day average exposures. We also found positive associations of ECG ST segment depression with exposure to outdoor home $PM_{2.5}$, BC, EC, OC, and to a lesser extent with exposure to outdoor CO and NO_x, but not PN. Associations were seen from lag 1 to a 6-day average. As with blood pressure, the strongest association was for OC, especially estimated fossil fuel combustion fraction (OC_{pri}).

Conclusions: A major implication of the exposure assessment findings is that, even if people (particularly the elderly retired population of our study) generally spend most of their time indoors, a major portion of the outdoor PM to which they are exposed comes from outdoor mobile sources.

In the epidemiologic analysis, we found traffic-related air pollutants near the home are associated with increased systemic inflammation, increased platelet activation, and decreased erythrocyte antioxidant enzyme activity, which may be partly behind air pollutant-related increases in systemic inflammation and thrombosis. Differences in association by period and particle size suggest components carried by ultrafine particles are important. The *in vitro* redox assay of concentrated $PM_{2.5}$ and $PM_{0.15}$ was not associated with biomarkers. This null result is most likely due to the limited sampling periods, although other unmeasured factors influencing activity could have affected results.

The significance of the indoor-outdoor exposure assessment findings is supported by the finding that compared with uncharacterized indoor PM, indoor infiltrated PM from mobile sources were more strongly associated with biomarkers among the subjects living in the studied retirement communities. This may not be the case for other people with major indoor sources of toxic air pollutants.

Findings from the study of both ambulatory blood pressure and ECG-detected ST segment depression suggest that traffic-related air pollution exposures are related to this response. This may increase risk of acute myocardial infarction in individuals with underlying CAD. Overall results suggest that current regulations of fine particle mass may not completely represent particle size fractions important to protect the public health of vulnerable populations such as the one studied. This likely includes particles <0.25 μm and pollutant components linked to fresh traffic emissions. However, CO and NO_x-NO_2 (routinely measured in California) functioned as good surrogates for associations with outcomes, even though levels did not exceed regulatory standards.